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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,685	09/19/2005	Eva Caroff	66535.000004	7434

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EXAMINER	
MANOHAR, MANU M	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
10/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,685	CAROFF ET AL.	
	Examiner	Art Unit	
	MANU MANOHAR	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-7,12 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,13,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The status of the Claim

Claims 1 – 21 are pending in this application. Original claims 1-21 were subjected to the election of species. The details are below.

Election and Restriction

Applicant's election of Group II (Claims 8-18) with traverse in the reply filed on July 07, 2008 is acknowledged. For the species election requirement the applicants elect a species of the compound N-[6-(3,4-Dimethoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazol-2yl]-guanidine. The traversal is on the ground(s) that the claimed compounds do contribute over the prior art. Applicants claimed that the claims recite compounds having particular chemical structure with specific exceptions. The applicants argue that the restriction requirement fails to set forth any specific findings as to how the particular claimed compounds are anticipated or obvious in view of the cited prior art. However the arguments are not found persuasive because of the rationale were presented in the restriction requirement mailed June 09, 2008.

Inventions, Group I, claims 1- 7, 19 and 20 are drawn to method of use, Group II, claims 8-18 are drawn to compound and compositions and Group III, claim 21, drawn to method of making. The inventions listed as Groups I-III do not relate to a single general

inventive concept and they lack the same or corresponding special technical features. The compounds in the claims 1-17, 20 and 21, Guanidine derivatives and the related compounds, do not contribute over the prior art. As stated in the communication for election restriction requirements the prior art teaches the use of the compounds from the same family as antagonist to histamine receptor which makes it obvious to use these derivatives as neuropeptide ff receptor antagonists. Therefore, unity of invention is lacking and restriction of the invention in accordance with the rules of unity of invention is proper. Hence the requirement of restriction and election of species is still deemed proper and is therefore made FINAL. In response to applicant's election Group I, claims 1- 7, 19 and 20 are drawn to method of use, Group III claim 21 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants have elected Group II (Claims 8-18) with traverse. However claims 8, 9, 10, 11, 17 and 18 which read on the elected species N-[6-(3,4-Dimethoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazol-2yl]-guanidine are only considered in the application. Claims 12, 13, 14, 15 and 16 are withdrawn from the considerations

Priority

The application is with a filing date of September 19, 2005. This application is a 371 of PCT/CH04/00175 with filing date of March 22, 2004 which claims the benefit of Switzerland 466/03 with the filing date of March 20, 2003 and examiner acknowledge the filing date. For this application the priority date is March 20, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 9, 10, 11, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is drawn to a compound of Formula I: in which A is a chain of 3-6 optionally substituted C atoms, one of which can be replaced by --O--, the ring skeleton containing only the two double bonds of the thiazole component; pharmaceutically applicable acid addition salts of basic compounds, pharmaceutically applicable salts of acid group-containing compounds with bases, pharmaceutically applicable esters of hydroxy or carboxy group-containing compounds as well as hydrates or solvates thereof

The term Formula 1 is not defined in the claim and the examiner is not clear about the chemical structure of the compound. The examiner assumes the formula I is

as stated in the claim 1 which is a non-elected claim and consider the Formula I in the claim I for further consideration.

Claim 11 recites the limitation 'compounds according to claim 10 in which the substituents is/are' and there is insufficient antecedent basis for this limitation in the claim 11. All the substituents stated in the claim 11 do not read on the compounds as stated in the claim 10.

Claims 8, 9, 10, 11, 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of pharmaceutical chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims".

a) the quantity of experimentation necessary: In the chemistry art it is not usually possible to predict the nature of the solvates, whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of

solvent added per molecule of host. Thus undue experimentation is necessary for the person skilled in the art to practice the invention- preparing the instant compound in solvate form.

b) The amount of direction or guidance presented: There is lack of enough guidance and direction to practice the invention – preparation of the solvates of the instant elected compound - in the specification of the application.

Preparation of solvates comprising the use different kind of solvents and the result would be unpredictable. Guidance for preparing and using of all the possible combinations reagent is not provided in the instant specification for preparation of solvates.

c) The presence or absence of working examples: There are several examples are included in the instant specification for preparing the derivatives of the instant compounds and other related compounds. However none of the examples describe the preparation solvates of the instant compound. As such, the practitioner would turn to trial and error experimentation in order to prepare the solvates of the instant compound without guidance from the specification.g) the predictability or unpredictability of the art: The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of a chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or

replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. Claims 9, 10, 11, 17 and 18 are also rejected which reads on the claim 8. (Even though your rationale is OK, you should address some more of the Wands factors listed above.)

Comment [m1]: I addressed the more Wands factors here. Thanks.

h) The breadth of the claims: The breadth of the claims includes all of the hundreds solvates of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is too broad and that is not supported by the specification.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." *In re Rainer*, 146

USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 9, 10 and 11are rejected under 35 U.S.C. 102(b) as being anticipated by Marinko et al (Tetrahedron Letters 42 8911-8913 2001). Claim 8 is drawn to a compound of Formula I: in which A is a chain of 3-6 optionally substituted C atoms, one of which can be replaced by --O--, the ring skeleton containing only the two double bonds of the thiazole component; pharmaceutically applicable acid addition salts of basic compounds, pharmaceutically applicable salts of acid group-containing compounds with bases, pharmaceutically applicable esters of hydroxy or carboxy group-containing compounds as well as hydrates or solvates thereof; with the exception of

N-(4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

(2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-yl)-ethyl acetate ethyl ester;

N-(4-hydroxymethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidin- e;

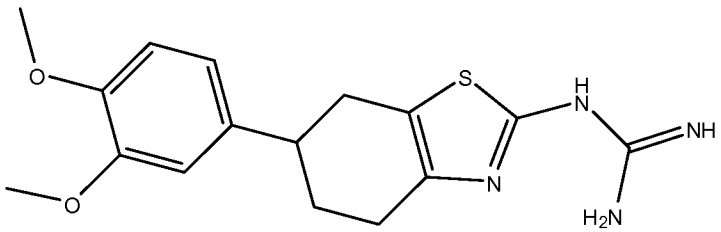
N-(4-tosyloxymethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

N-(4-azidomethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

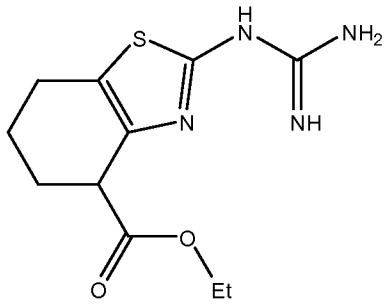
N-(4-aminomethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine; and

N-(6-acetylaminomethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine.

The applicant elected the species N-[6-(3,4-Dimethoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazol-2yl]-guanidine the structure is shown below.



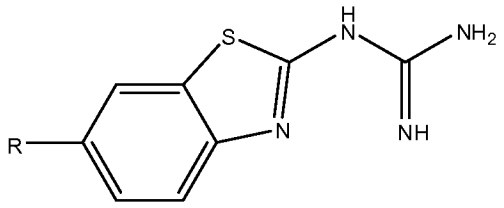
The elected species is free of prior art, however, Marinko et al teaches core structure of instant compound (page 8912, Scheme 1, Formula 6b) and the structure can read on related species of the genus - guanidine derivatives. The Structure is shown below



Claim 8 is rejected based on the anticipation of the core structure by Marinko et al. Claims 9, 10 and 11, the dependent claims of claim 8, which reads on the structure taught by Marinko et al are also rejected.

Claims 8, 9, 10, 11, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Morain et al, (Mol. Pharmacology 46 732-742 1994).

As stated above, claim 8 is drawn to the structure of Guanidine derivative and the elected species, N-[6-(3,4-Dimethoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazol-2yl]-guanidine, as shown in the structure above. Morain et al teaches basic structure of instant compound (Page 733 the structure above table 2) and the structure can read on the species of the genus, guanidine derivatives. The structure taught by Morain et al is shown below.



Claim 17 is drawn to a therapeutic composition comprising the compound according to claim 8. Claim 18 is drawn to a medicinal product, comprising a compound according to claim 8 and an inert carrier. Morain et al teaches the preparation of test compounds (guanidine derivatives) with various composition and the medium (page 734 column 1 first paragraph) and these compounds are used as agonist for 5-Hydroxytryptamine receptor, medicinal product (page 732 summary). Also Morain et al inherently teaches the medium and solvents are non-reactive, thus inert carrier.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MANU MANOHAR whose telephone number is (571)270-5752. The examiner can normally be reached on Mon - Thu 9.00AM to 4.00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (I don't know the correct Fax Number) 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR)

system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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MM

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